Avellino Corneal Dystrophy after LASIK

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Objective: To report cases of Avellino corneal dystrophy (ACD) exacerbated by LASIK for myopia.

Design: Retrospective, noncomparative, interventional case series and review of the literature.

Participants: Seven patients.

Intervention: Six patients with exacerbation of granular corneal deposits after LASIK were examined for TGFBI mutations by polymerase chain reaction sequencing of DNA. One previously reported patient who was heterozygous for the ACD gene was followed up for 16 months after mechanical removal of granular deposits from the interface after LASIK.

Main Outcome Measures: Slit-lamp examination, visual acuity, manifest refraction, and DNA sequencing analysis.

Results: All patients were heterozygous for the Avellino dystrophy gene. Corneal opacities appeared 12 months or more after LASIK. Best spectacle-corrected visual acuity decreased as the number and density of the opacities increased. One patient underwent mechanical removal of granules from the interface and had a severe recurrence within 16 months. Another patient had removal of the granules from the interface with PTK, followed by treatment with topical mitomycin C. In this patient, the cornea has remained relatively clear for 6 months.

Conclusions: Laser in situ keratomileusis increases the deposition of visually significant corneal opacities and is contraindicated in patients with ACD. Mechanical removal of the material from the interface does not prevent further visually significant deposits. Mitomycin C treatment, in conjunction with surgical removal of opacities, may be an effective treatment. Ophthalmology 2004;111:463–468 © 2004 by the American Academy of Ophthalmology.

Avellino corneal dystrophy (ACD) is an autosomal dominant dystrophy with clinical features of both granular and lattice dystrophy. Originally described in patients from Avellino, Italy, it has now been reported around the world.1–5

Its appearance is variable, and it is often misdiagnosed as granular dystrophy.6–8 The diagnosis can be confirmed by genetic analysis, demonstrating the replacement of histidine by arginine at codon 124 of the TGFBI gene.9,10 In patients with heterozygous ACD, the deposition of corneal opacities generally is slow, and good visual acuity is maintained until later life despite an increasing number of granular opacities in the cornea. Patients with homozygous ACD typically have an earlier onset of visual symptoms and granular opacities, with increasing lattice-like deposits in later life.1,11

We recently reported a patient with heterozygous ACD in whom corneal deposits increased after LASIK.12 In that case report, the deposits appeared in the interface and were removed 21 months after LASIK, with an improvement in best spectacle-corrected visual acuity (BSCVA).12

The purpose of this study was to report 6 additional patients with ACD who underwent LASIK and to provide additional follow-up on the previously reported patient.

Patients and Methods

Seven patients with white granular opacities in the interface between the flap and stromal bed after uneventful LASIK are the subjects of this report. Preoperative characteristics of each and details of the surgeries are shown in Table 1.

DNA analysis was performed from peripheral blood as previously described.12 The TGFBI gene was analyzed by sequencing exon 4 for ACD (R124H mutation) and exon 12 for granular corneal dystrophy (R555W mutation). The primer pairs used to amplify the 2 exons were purified with a polymerase chain reaction purification kit (Qiagen, Hilden, Germany) and were sequenced with an automatic fluorescent DNA sequencer (ABI Prism 377; Applied Biosystems, Foster City, CA) and a dry terminator cycle sequencing kit (Perkin Elmer, Foster City, CA). All 7 patients were heterozygous for the ACD gene.
Patient 1

A 33-year-old Korean male underwent LASIK in 1996. An ophthalmic examination performed 6 years previously did not document corneal opacities. Manifest refraction (MR) before LASIK was −9.00 −0.50×90 in the right eye and −9.50 in the left eye, yielding 20/20 in the right eye and 20/25 in the left eye. Fourteen months after surgery, the surgeon noted white opacities in the interface between the flap and the residual stromal bed in both eyes, even though the BSCVA was 20/20 in both eyes. The patient visited another physician, who removed some of the opacities from the interface of the left cornea on September 9, 2002.

On presentation on October 24, 2002, granular deposits were observed centrally in the interface beneath the flap of both eyes, more numerous in the right than in the left. Manifest refraction was −3.25 −0.50×40 in the right eye and −2.50 −1.00×90 in the left eye, yielding 20/30 in the right eye and 20/40 in the left eye.

His 61-year-old father and 1 of his 2 sisters had corneal opacities consistent with ACD. Another surgeon had declined to perform LASIK on that sister with ACD 4 years previously at her age of 26 because white granules were observed in the corneal stroma. That same surgeon performed LASIK on the other sister, who was 24 years old at the time, because no stromal opacities were noted. At our examination, we confirmed that the sister who had LASIK 4 years ago had no abnormal corneal deposits, and her DNA sequencing showed a normal TGFBI gene.

Patient 2

A 27-year-old Korean female who had undergone LASIK in the left eye 5 years previously was referred in October 2002 for decreased visual acuity in the operated eye.

Before LASIK, MR was −6.00 −1.50×180 in the right eye and −9.50 −2.50×5 in the left eye, yielding 20/20 in the right eye and 20/25 in the left eye. A few granular corneal opacities were observed before LASIK in both eyes. Surgery was performed uneventfully, and uncorrected visual acuity in the left eye was 20/25 4 months after LASIK. The ethics committee of that hospital prohibited the surgeon from performing LASIK on the opposite eye because of the appearance of granular opacities in the operated eye.

In January 2002, the patient noted blurred vision in the left eye. On presentation, there were several discrete granular opacities in the anterior stroma of right cornea. Manifest refraction and BSCVA of the right eye were unchanged from 5 years previously. In the operated left cornea, numerous dense, confluent granular opacities were noted centrally in the interface between the flap and residual stroma (Fig 2). Manifest refraction was −1.50 in the left eye, yielding 20/100 BSCVA.

Patient 3

A 32-year-old Korean female was referred in July 2002 with decreased visual acuity in her right eye. She had undergone LASIK in both eyes 4 years previously, without complications. Several granular corneal opacities had been observed in both eyes before surgery. Two years after LASIK, she noted progressive loss of vision.

On presentation, MR was −5.00 +1.75×95 in the right eye and −1.25 +1.50×90 in the left eye, yielding 20/40 in the right eye and 20/20 in the left eye. Numerous fine, white, stromal granular deposits were observed centrally in the interface between the flap and residual stroma, more numerous on the right than the left.

Her father was found to have ACD, whereas her mother, 2 brothers, and a sister had clear corneas. Her sister, who had undergone LASIK 4 years previously at the age of 25 years, had clear corneas and a normal TGFBI gene sequence.
Figure 1. Patient 1. Fine, white, granular deposits in the interface of the central zone 7 years after LASIK. The photo was obtained before the removal of some opacities of the left cornea. A, Right eye. B, Left eye.

Figure 2. Patient 2. A, Discrete granular opacities in the anterior stroma of the unoperated eye (right eye) 5 years after LASIK in the opposite eye. B, Numerous dense, confluent granular opacities are seen centrally in the interface between the flap and residual stromal bed of the operated eye (left eye) 5 years after LASIK.

Figure 3. Patient 5. A, Preexisting discrete granular opacities in the stroma and numerous fine granular opacities in the interface between the flap and residual stroma 26 months after LASIK (left eye). B, Three months after treatment with phototherapeutic keratectomy and mitomycin C, the cornea was nearly clear, except for the preexisting granular opacities (left eye).
Patient 4
A 34-year-old Korean female was referred in November 2002 for blurred vision in her right eye 24 months after uncomplicated bilateral LASIK. On presentation, numerous fine, white, granular deposits were noted in the right cornea. The left eye showed a few granular deposits and faint white opacities in the interface. Manifest refraction was 0.00 Δ +0.25 Δ 180 in the right eye and +0.25 Δ 180 in the left eye, yielding 20/25 visual acuity in both eyes. The preoperative MR was 9.25 Δ 2.00 Δ 180 in the right eye and 8.25 Δ 1.00 Δ 15 in the left eye, yielding 20/20 visual acuity in both eyes. Several discrete granular corneal opacities were observed in each eye. The patient’s father and 2 sisters had clinical evidence of ACD. One of the sisters received a phakic intraocular lens 1 year prior, and there have been no abnormal deposits in the central cornea or the healed incision.

Patient 5
A 28-year-old Korean female was referred with decreased visual acuity in the right eye in June 2001, 13 months after uncomplicated bilateral LASIK. On presentation, numerous fine, white, granular deposits were noted in the right cornea. The left eye showed a few granular deposits and faint white opacities in the interface. Manifest refraction was 1.00 Δ +1.00 Δ 85 in the right eye and −8.25 Δ −1.00 Δ 15 in the left eye, yielding 20/20 visual acuity in both eyes. Several discrete granular corneal opacities were observed in each eye. The preoperative MR was −9.25 Δ −2.00 Δ 180 in the right eye and −8.25 Δ −1.00 Δ 15 in the left eye, yielding 20/20 visual acuity in both eyes. Several discrete granular corneal opacities were observed in each eye. Granular opacities increased in density in both eyes (Fig 3). The patient’s visual acuity decreased to 20/50 in the right eye and 20/200 in the left eye 26 months after LASIK. One of the authors (HWC) lifted the left corneal flap and performed phototherapeutic keratectomy on the remaining posterior stromal bed (5.0 mm in diameter and 23 μm in depth) and posterior surface of the flap (5.0 mm in diameter and 23 μm in depth). Mitomycin C 0.02% then was applied for 2 minutes to the stromal bed and posterior surface of the flap. Three months after the procedure, the BSCVA of the left eye improved to 20/20 without recurrence of opacities (Fig 3) and remained the same until 6 months after the procedure. Her mother had clinical evidence of ACD, whereas her father, 2 brothers, and a sister had clear corneas.

Patient 6
A 28-year-old Korean female was referred for night-time glare in her right eye in July 2002, 12 months after uncomplicated bilateral LASIK. Before surgery, MR was −9.50 Δ −7.75 Δ −1.50 Δ 180 in the right eye, yielding a visual acuity of 20/20 in both eyes. Several discrete granular corneal opacities were observed in each eye. On presentation, numerous fine, white, anterior stromal granular deposits were observed in the interface between the corneal flap and residual stroma of each eye. The deposits in the right cornea patient began to report decreased visual acuity and glare 5 months after surgery that gradually worsened. The granular opacities increased in density in both eyes (Fig 3). The patient’s visual acuity decreased to 20/50 in the right eye and 20/200 in the left eye 26 months after LASIK. One of the authors (HWC) lifted the left corneal flap and performed phototherapeutic keratectomy on the remaining posterior stromal bed (5.0 mm in diameter and 23 μm in depth) and posterior surface of the flap (5.0 mm in diameter and 23 μm in depth). Mitomycin C 0.02% then was applied for 2 minutes to the stromal bed and posterior surface of the flap. Three months after the procedure, the BSCVA of the left eye improved to 20/20 without recurrence of opacities (Fig 3) and remained the same until 6 months after the procedure. Her mother had clinical evidence of ACD, whereas her father, 2 brothers, and a sister had clear corneas.
were more numerous than those in the left. Manifest refraction was +0.25 +0.25×90 in the right eye and 0.00 +0.25×90 in the left eye, yielding a visual acuity of 20/25 in both eyes.

The family history was not known.

**Patient 7**

This 23-year-old Korean female had white granular opacities in the interface between the corneal flap and residual stroma 12 months after LASIK. The flaps were lifted, and the opacities were scraped from the interface 21 months after LASIK because of decreased visual acuity and decreased contrast sensitivity.12 One month after removal of the opaque material from the interface, BSCVA improved to 20/20 in the left eye, and contrast sensitivity returned to normal. Opaque material continued to be deposited afterward. Six months after removal of the opacities, BSCVA was 20/30 in the right eye and 20/25 in the left eye.

Sixteen months after removal of the opacities, BSCVA of left eye decreased to 20/50. The opacities in both corneas continued to increase, more rapidly in the left than the right (Fig 4). The opacities were located mainly in the central ablated cornea, but some also were observed in the area outside of the laser ablation (data not shown). Contrast sensitivity of left eye worsened, whereas contrast sensitivity of the right eye was unchanged.

**Discussion**

We report worsening of corneal opacities in 7 patients with ACD who underwent LASIK. In patient 2, only a few deposits were observed in the corneal stroma of the unoperated eye, whereas numerous opacities were observed in the operated cornea (Fig 2). The corneas of patients 1 and 3 showed numerous opaque deposits, whereas the corneas of their siblings with no ACD gene remained transparent after LASIK. These observations show that the ACD gene itself is related to the deposition of granular corneal opacities in patients with ACD who undergo LASIK.

As can be seen from Table 1, deposits were observed after LASIK with multiple brands of laser and microkeratome. The ACD deposits appeared mainly within the ablation zone, suggesting that the deposition of corneal opacities may be related to corneal trauma created by an excimer laser.

Corneal opacities that appear in patients with ACD after LASIK are composed of hyaline,12 which is the material found in the opacities of ACD and granular dystrophy.8,13 Avellino corneal dystrophy contains a mutation in the **TGF-B1** gene, which is activated by transforming growth factor-β (TGF-β),12 and corneal wounds are associated with an increase in the production of TGF-β.15–18 Kaji et al19 reported that TGF-β1 was detected in the rabbit cornea after photorefractive keratectomy, whereas it was not detected after LASIK, suggesting that the expression of TGF-β1 would be lower after LASIK than after photorefractive keratectomy. We postulate that the creation of a corneal flap and the removal of tissue with the laser caused an increase in the production of cytokines possibly including TGF-β, which leads to the slow deposition of hyaline observed more than 1 year after the procedure in patients with ACD. Scraping of the opacities from the interface in patient 7 caused more severe deposition of opacities in a shorter interval after surgery than was seen after the primary procedure. Some of the opacities were deposited outside of the ablation zone. We hypothesize that the additional trauma of lifting the flap and mechanically removing the opacities increased the production of cytokines further and led to the deposition of even more opacities.

Both phototherapeutic keratectomy (PTK) and LASIK are procedures that traumatize the cornea. After PTK in patients with heterozygous ACD, the deposition of mild, punctate opacities has been observed in the central superficial cornea.20 Mashima et al21 reported a heterozygous ACD case with diffuse opacities that appeared at the host–graft interface in the pupillary area 4 years after lamellar keratoplasty. In our report, opacities were observed centrally in the interface between the flap and residual stroma after LASIK. This may be explained by the presence of a potential space that may trap material beneath the flap after LASIK, in contrast to PTK, after which no potential space exists.

Holland et al1 reported that patients with heterozygous ACD tend to experience unilateral opacities between the ages of 6 and 16 years and tend to experience bilateral opacities thereafter. In this report, granular corneal opacities were documented before surgery in the medical records of all subjects except in that of patient 1, who was 27 years of age at the time of LASIK procedure. His father and 26-year-old sister had obvious corneal opacities, however, leading us to suspect that subtle stromal opacities may have been present in the patient at the time of LASIK. The available pedigrees in our series (for patients 1, 3, 4, 5, and 7) showed an autosomal dominant inheritance pattern for ACD. A family history, slit-lamp examination of family members, or ACD gene analysis all may be useful in avoiding LASIK in patients with ACD.

The density and number of deposits varied among the patients in this study. Patients 3 and 4 had diffuse opacities, whereas the others had granular deposits. The appearance of the corneas of our patients who underwent bilateral surgery was bilaterally asymmetrical, and recurrent opacities were noted 1 to 5 years after LASIK. This variability in morphologic features and the course of deposition is consistent with the varied expression of ACD in unoperated corneas. Konishi et al8 described 2 phenotypes of ACD. 1 characterized by discrete deposits in the anterior stroma with star-shaped deposits in the deeper stroma and the other characterized by linear and granular deposits accompanied by a central diffuse opacity. Watanabe et al22 described 2 different phenotypes of the homozygous R124H mutation. The type I pattern consists of confluent spotlike opacities in the anterior stroma, whereas the type II consists of reticular opacities in the anterior stroma with round translucent spaces. Avellino corneal dystrophy has a wide spectrum of phenotypic expression that may be influenced by genetic background.

Surgical removal alone was not effective in preventing the continued deposition of corneal opacities after LASIK (patient 7). Mitomycin C, which has been used for the treatment of scarring after photorefractive keratectomy,23–25 seemed to be effective in preventing an exacerbation of ACD after interface opacities were removed with PTK.
(patient 5; Fig 3). Follow-up of this patient was limited to 6 months, however, and additional experience will be required to confirm its safety and efficacy. Anti-TGF-β may be another approach to the treatment of recurrent ACD after LASIK and other corneal trauma, and phakic intraocular lenses are an alternative form of refractive surgery that can be offered to patients with ACD.

These cases support our previous statement that LASIK is contraindicated in patients with ACD because it results in the deposition of granular corneal opacities and reduces BSCVA. Removal of the material from the interface is not recommended unless it is accompanied by treatment with topical mitomycin C. Further observation will be necessary to determine the long-term safety and efficacy of mitomycin C treatment for recurrent ACD after LASIK and the safety of LASIK in patients with other types of corneal dystrophies.

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References